IV. NICOTINE PHARMACODYNAMICS

In this section we will discuss the actions of nicotine on the nervous system and on behaviour which may be used to account for the smoking habit. The literature is vast and so only illustrative experiments will be cited. In the first section the emphasis will be on the neurochemical changes that are produced by smoking doses of nicotine. In the second section the neurophysiological effects of nicotine will be outlined. In the third section these changes will be related to nicotine's effect on psychophysiological measures that have been associated with behaviour. The final, fourth section will discuss nicotine's action on human behaviour - the psychopharmacology of nicotine.

A. Neurochemical Action of Nicotine

Nicotine could modify neural transmission by interfering with one or more of the processes that are responsible for the regulation of transmitters ie (1) Alter transmitter synthesis by either changing the availability of transmitter precursors or changing the activity of the synthesising enzyme. (2) Interfere with the presynaptic storage of the transmitter. (3) Modify transmitter release into the synapse. (4) Alter the rate of transmitter inactivation by modifying the inactivating enzyme or the presynaptic reuptake (Warburton, 1975).

There is evidence in the literature from in vivo animal studies that nicotine produces changes in the brain levels of catecholamines, indoleamines and acetylcholine. The crucial questions are how can these changes in levels be related to the dynamics of transmitter systems and whether these changes can be extrapolated meaningfully to humans to explain the smoking habit.

A major problem, with the majority of these animal studies, is the unrealistically high dose levels of nicotine that have been tested. A 75 kg person, who takes between 0.75 and 3.0 mg of nicotine from a cigarette into his mouth, will receive a dose of between 10 and 40 µg per

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kg. This figure is close to that derived by Armitage (1974) who calculated that the dose inhaled from each puff by a smoker is equivalent to an intravenous injection of 1 to 2 µg per kg. Assuming about 10 to 20 puffs per cigarette, this will give a dose of between 10-40 µg per kg per cigarette. There will obviously be differences because of the route of administration (inhalation and intravenous injection versus subcutaneous and intraperitoneal injection) and the different metabolic rates of different species, but it is probably safe to conclude that in mice, rats or cats, any dose which is over 10 times this dose (0.4 mg/kg) is well outside the "smoking" dose range.

1. Catecholamines

Studies on the catecholamines, dopamine and noradrenalin have been carried out by Lichtensteiger and his co-workers (Lichtensteiger, Felix, Lienhart and Hefti, 1976; Lichtensteiger, Richards and Koppe, 1978; Lichtensteiger, 1979) by Fuxe and his colleagues (Fuxe, Agnati, Eneroth, Gustafson, Hokfelt, Lofstrom, Skett and Skett, 1977; Eneroth, Fuxe, Gastafson, Hokfelt, Lofstrom, Skett and Agnati, 1977 a and b) and Westfall's laboratory (Westfall, Fleming, Fudger and Clark, 1967; Westfall, 1974).

These studies have given the same general picture in spite of wide differences in nicotine dose levels, which ranged from 0.33 mg/kg in one of Lichtensteiger's studies to four doses of 3 mg/kg at 30 min intervals in one of the experiments of Fuxe's group. Lichtensteiger reported that the fluorescence intensity of both dopamine and noradrenalin neurones was increased in the substantia nigra nuclei, zona compacta and zona incerta with doses of 0.33 mg/kg and 1.00 mg/kg of nicotine, suggesting increased activity in these neurones. This conclusion was supported by microelectrode recording of the neurones and biochemical analysis which showed some depletion of both transmitters. Westfall has also found that dopamine was reduced in the striatum of the mouse after 1 mg/kg of nicotine injected intraperitoneally.

Lichtensteiger also reported increased fluorescence of dopamine neurones in the rat median eminence of the diencephalon after 1 mg/kg

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of nicotine and Westfall had previously found that this dose produced about 20 per cent depletion of noradrenalin in the same region in the mouse. Both of these findings would be consistent with increased neuronal activity in these catecholamine neurones and Lictensteiger demonstrated, with microelectrodes, that there was increased neural activity in this region as well as decreased growth hormone and prolactin secretion in the blood stream (dopamine is thought to be involved in the secretion of these hormones). There was also some evidence which was compatible with nicotine activating dopamine neurones controlling luteinizing hormone release.

Fuxe and his group investigated the specific relation between nicotine, catecholamines and gonadotrophin secretion. Unfortunately, they used large doses of 1 mg/kg, 2 mg/kg and 3 mg/kg injected four times in 90 mins before sacrifice and assay. Nicotine produced a depletion of 25 per cent in catecholamine levels in the median palisade zone of the median eminence of male rats (Fuxe et al, 1977) but hexamethonium prevented depletion. No changes were found in dopamine or noradrenalin receptor activity in in vitro studies so the changes are secondary to effects on cholinergic neurones. They also observed a reduction of luteinizing hormone and prolactin secretion in female rats. The implication of these findings for human smoking is dubious due to the very high doses that were used and it would be quite wrong to conclude from this data alone that nicotine could produce hormonal problems in pregnant and lactating women who smoked.

2. Indoleamines

Changes in the concentration and turnover of serotonin have been found after doses of nicotine. A dose of 1 mg/kg of nicotine, intraperitoneally injected into mice, markedly increased the levels of serotonin in the mesencephalon and diencephalon within 15 mins but not in the cortex (Essman, 1971). In the same study serotonin's major metabolite, 5-hydroxyindoleacetic acid, was also increased but there was a decreased serotonin turnover rate of 20 per cent and increased serotonin turnover time (+300 per cent). These data are not simple to interpret but clearly with this moderately large dose there are increased serotonin levels in some brain regions

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probably due to increased synthesis and decreased release but, in spite of the decreased release, the large intraneuronal accumulation results in some leakage which elevates the level of 5-hydroxyindoleacetic acid. It is not clear whether the changes in serotonin after a moderately large dose of nicotine are important for human smoking.

3. Acetylcholine

Nicotine depletes whole brain acetylcholine in the rat (Pepeu, 1965) and mouse (Essman, 1971) in doses of 1 mg/kg. Depletion of transmitter could be a consequence of decreased synthesis, increased release from storage, increased release into the synaptic cleft or more effective enzymatic activation. There is no evidence that nicotine modifies acetylcholine synthesis (Hrdina, 1974) and the enzymatic inactivation of acetylcholine without any drug is extremely effective, which argues for a change in either storage of release. More importantly, there is strong evidence for increased free acetylcholine at the cortex after a "smoking" dose (40 µg/kg intravenously) in the cat (Armitage, Hall, Sellers, 1969) which is consistent with these two hypotheses.

The question of nicotine-induced changes in acetylcholine storage pools was tackled by Essman (1971). He found evidence of a decrease of acetylcholine in synaptic vesicles and in bound acetylcholine at the neocortex which suggests that acetylcholine was being released from storage by nicotine. However there was no increase in the free acetylcholine pool concentration which argues for increased release of the unbound transmitter and subsequent inactivation by acetylcholinesterase. The phenonemon of increased release at the cortex would be explained if nicotine enhanced presynaptic release mechanisms in cortical tissue but there is no in vitro evidence of enhancement (Hrdina, 1974). Thus we are left with the hypothesis that it is increased activity in the cholinergic neurones to the cortex which produces the in vivo depletion.

4. Conclusion

There is evidence that moderate to enormous doses of nicotine cause changes in catecholamines and indoleamines although the catecholamine changes were being mediated by cholinergic pathways. However, as

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Domino (1973) pointed out in a review of the behavioural studies, we must be cautious:- "The relevance of such large doses of nicotine given subcutaneously to the much smaller doses inhaled by man is certainly to be questioned" (P10).

The major effect with "smoking" doses has been to increase cortical release of acetylcholine but there is no evidence that release is due to a direct effect on the presynaptic release mechanisms of cortical neurones. One solution to the paradox lies in indirect activation of acetylcholine neurones which form part of the ascending cholinergic pathways to the cortex; this is discussed in the next section.

B. Neurophysiological Action of Nicotine

The action of many drugs has been explored by using the more readily accessible neurones in the peripheral nervous system which are more accessible than those in the central nervous system. Although caution must be exercised when using this data to explain central nervous system phenomena, in general, the principles that have been derived from such studies have proved useful in understanding the action of drugs on the brain. Thus the first studies will describe nicotine's action on these neural junctions.

1. Peripheral Nervous System

The action of nicotine on the nervous system has been known since the pioneering work of Dale who published a classic paper on acetylcholine "The action of certain esters and ethers of choline and their relation of muscarine" (Dale, 1914). This work established that nicotine mimicked the action of acetylcholine at autonomic ganglia and neuromuscular junctions and later it was established that acetylcholine was a transmitter at these synapses. Dale's work also revealed that some acetylcholine synapses, the post-ganglionic parasympathetic neurones, were better stimulated by muscarine than nicotine, and so it has become conventional to sub-divide peripheral nervous system neurones into "nicotinic" and "muscarinic" on the basis of their differential sensitivity to these two agonists - the two sorts of agonists that have been discovered. These neurones

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differ in the post-synaptic receptors as defined by Furchcott (1964):- "The specific molecular sites in (or on) the effector cell with which the molecules of a specific agonist must react in order to elicit the characteristic response of the cell to the agonist". In the case of nicotine the characteristic response is postsynaptic depolarization.

The effects of different doses of nicotine on cell membrane depolarization and subsequent action potentials were compared by Paton and Perry, (1953) using the cervical ganglion preparation of the cat. The drug was injected into the external carotid artery and all branches of the common carotid were blocked except the arterial branches supplying the ganglion itself, and the occipital artery to allow free blood flow past the ganglion. Then 0.2 ml of the solution containing 50 µg of nicotine tartrate was injected into the external carotid artery. This concentration is much larger than the 20-30 ng/ml found in the forearm vein after smoking (see Section II) but may be closer to the concentration ascending in the carotid artery after inhalation because none of this nicotine will have been metabolised. The effect of this dose was depolarization of the membrane and some reduction of the subsequent action potentials, a change which was similar to, but more transient than, the effects of a small dose of acetylcholine.

However 0.3 mg of nicotine, six times the above dose, produced prolonged depolarization and the action potentials were abolished ie ganglionic blocking. A challenge with a second dose of nicotine after the origianl depolarization, but before recovery of the action potentials, produced less depolarization than previously which demonstrated that nicotine was producing a competitive block of cholinergic receptors at very high doses. Exactly the same phenomenon has been observed with high doses of acetylcholine at the motor end-plate so that once again nicotine is mimicking acetylcholine. It has been suggested that the desensitization arises from the transformation of the acetylcholine receptor complex into an inactive form (Katz and Thesleff, 1957) and that the same effect occurs with nicotine. Whatever the reason, it seems unlikely that blood concentrations some 100,000 times that found in the human forearm vein ever occur in the smoker's brain and hence unlikely that a depolarization block occurs in brain neurones after nicotine. In summary, "smoking" doses of

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nicotine precisely mimic acetylcholine and produce the same neural changes that would occur after natural activation of that synapse.

The reason for the exact mimicking of acetylcholine by nicotine at some cholinergic synapses is the remarkable similarity between the structures of the two molecules. Analysis by X-ray diffraction crystallography has shown that in order to interact with nicotine receptors, a molecule must consist of a planar acetoxy group or an aromatic ring separated from a methylated ammonium group which is about 130 picometres above the plane of the planar group (Pauling, 1970). Nicotine does consist of a planar pyridine ring perpendicular to the four coplanar atoms of the pyrollidine ring. Both nicotine and acetylcholine have a positively charged, methylated, tertiary nitrogen group (N^+-CH_3) in the pyrollidine ring which in nicotine is attached to an electronegative, isosteric nitrogen in the pyridine ring at just the distance to match the electronegative carbonyl oxygen of acetylcholine (see Figure 1).

2. Adrenal Medulla

One preganglionic nerve, the lesser splanchnic nerve, continues without synapses to the medulla of the adrenal gland. The adrenal medulla can be considered as an aggregation of specialised postganglionic cells which releases catecholamines into the bloodstream instead of releasing noradrenalin at its terminals onto other organs. Adrenalin is the major hormone that is released into the circulation to act on target cells while noradrenalin is mainly a neurotransmitter although the plasma levels can rise to concentrations which produce hormonal effects, for example, after heavy exercise.

Both catecholamines trigger haemodynamic effects; both raise blood pressure and dilate coronary vessels but adrenalin alone dilates skeletal muscle vessels. The rise in blood pressure is due to vasoconstriction of vessels of the skin, mucous membranes and viscera. The catecholamines have no direct effect on blood flow in the brain although an adrenalin solution of high concentration produces a sudden rise in systolic and diastolic pressure which can cause cerebral haemorrhage. The

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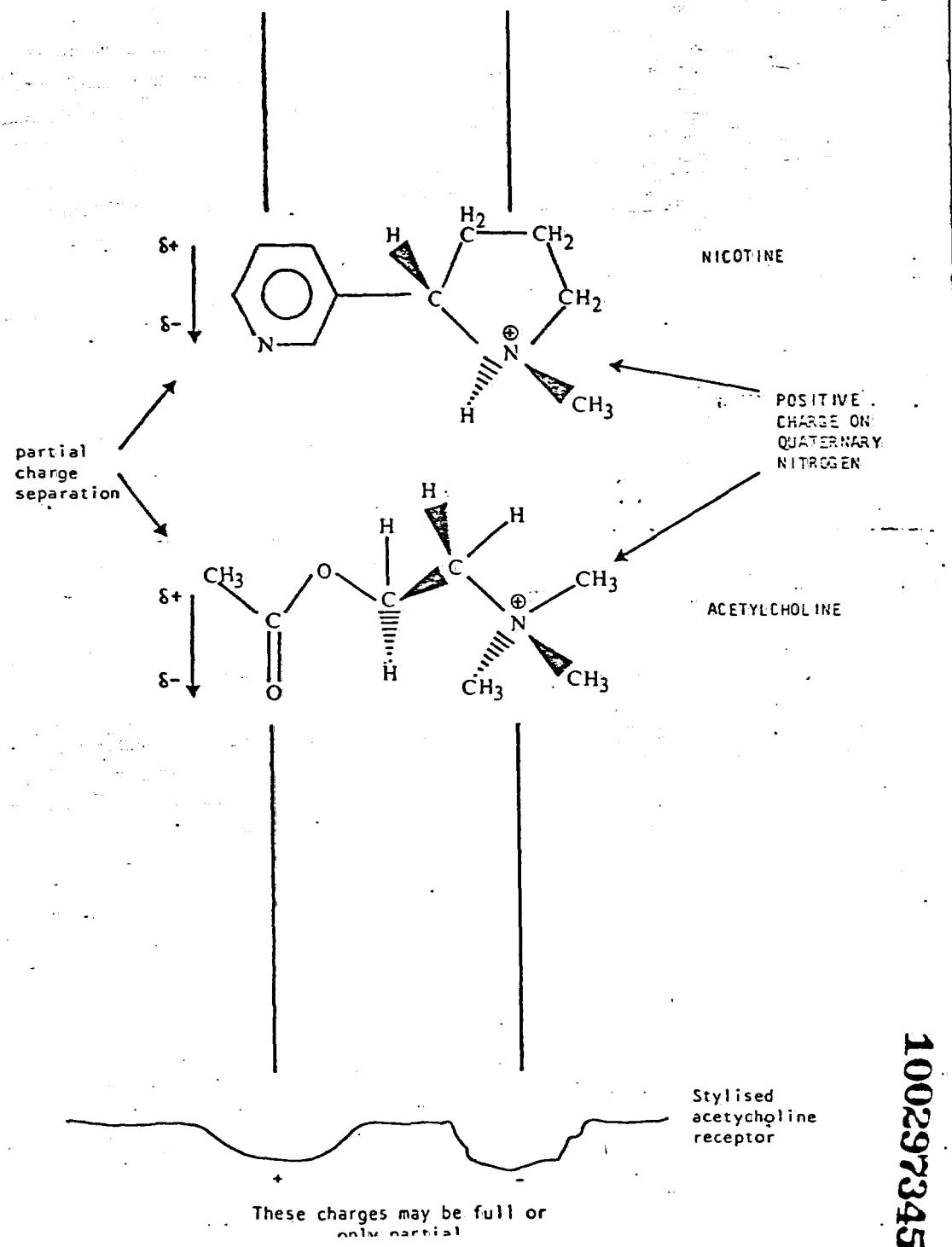
NICOTINE AND ACETYLCHOLINE



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catecholamines have powerful effects on the heart increasing the shape of the pacemaker potential so that the firing threshold is reached more quickly and heart rate increases. It also increases the strength of heart rate contraction.

Of special interest are the metabolic effects of catecholamines. They accelerate delivery of glucose from the liver, reduce glucose clearance from the circulation and, as a consequence, the plasma levels of glucose rise. In addition the catecholamines stimulate lipolysis, increasing the delivery of free fatty acids to the liver. In the liver they may also act on hepatic metabolic processes to stimulate ketogenesis, which fuels those cells which do not depend on carbohydrates, and supplies glycerol for use in glucose synthesis. The increased free fatty acids will also reduce glucose uptake and use by cells with flexible metabolic requirements.

Classically these changes have been linked to the dramatic behaviour of flight or fight but the hormones have a much broader function. They are released when the person is anxious, concentrating hard, kissing or just changing from a lying down to sitting position; elevation of catecholamines does not necessarily indicate distress or unpleasant circumstances.

Smoking a single cigarette elevates both plasma noradrenalin and adrenalin within five minutes of starting the cigarette and they peak at, or soon after, the maximum plasma nicotine level is reached, see Figure 2 on page 39:

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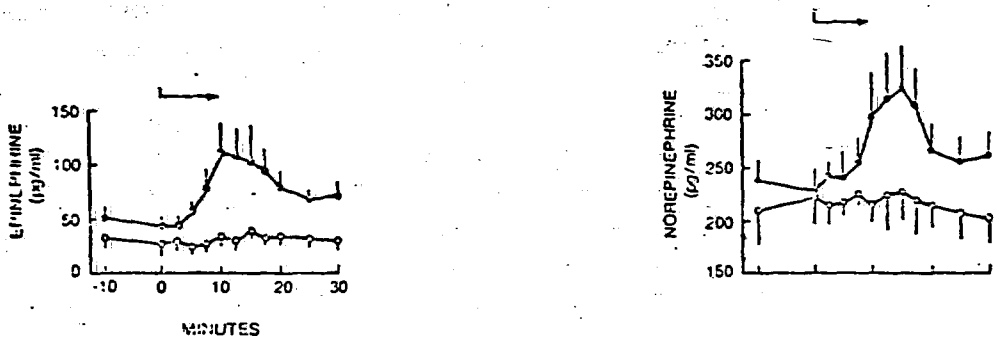
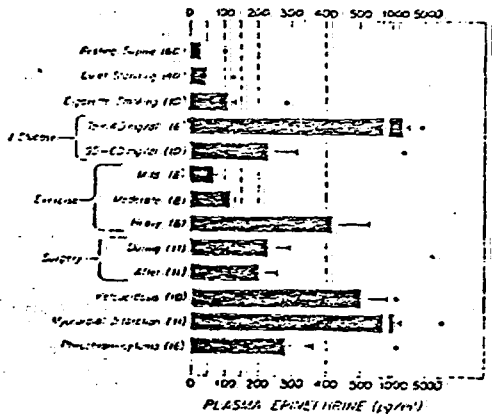
Figure 2

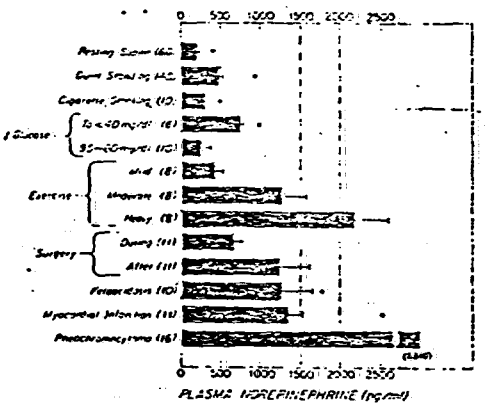


Mean (± S.E.) plasma norepinephrine and epinephrine concentrations in association with smoking (closed symbols) and sham smoking (open symbols). The arrows indicate the period of smoking (or sham smoking).



Venous Plasma Levels of Epinephrine in Human Beings in Various Physiologic and Pathophysiologic States (Mean ±S.E.M.).

Numbers in parentheses indicate the number of persons studied, solid circles represent the highest value observed. Dashed lines indicate the ranges of concentrations required to produce measurable changes in heart rate, systolic blood pressure, and blood glycerol (about 50 to 100 pg per milliliter), increases in plasma glucose, blood lactate, blood beta-hydroxybutyrate, and diastolic blood pressure (about 150 to 200 pg per milliliter), and initial decreases in plasma insulin (more than 400 pg per milliliter) in normal human subjects.[8]



Venous Plasma Levels of Norepinephrine in Various Physiologic and Pathophysiologic States in Human Beings (Mean ±S.E.M.).

Numbers in parentheses indicate the number of persons studied; solid circles represent the highest value observed. Dashed lines encompass the range of concentrations required to produce measurable metabolic and hemodynamic changes in normal subjects.[8]

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The peak plasma concentration for noradrenalin is 330-350 pg/ml and for adrenalin it is 100-140 pg/ml (Cryer, Haymond, Santiago and Shah, 1976). These levels must be considered in the context of the levels for other activities (Cryer, 1980). It can be seen that cigarette smoking produces higher levels of noradrenalin than resting supine, but less than quiet standing and mild exercise and certainly less than moderate and vigorous exercise. A slightly different pattern is seen with adrenalin levels after smoking; they are about the same as after moderate exercise and greater than resting supine, quiet standing and mild exercise, but about a quarter of the levels seen after heavy exercise, over 400 pg/ml. Cryer (1980) has used graded infusions of noradrenalin and adrenalin to discover the threshold levels for haemodynamic and metabolic changes and found that smoking produces suprathreshold elevations of adrenalin but not noradrenalin. The adrenalin thresholds were 50-100 pg/ml for increased heart rate, 75-125 pg/ml for systolic pressor effects and lipolysis and 150-200 pg/ml for ketogenesis and glycolysis changes (see Figure 2).

In summary, nicotine, from a single cigarette, produces small increases in plasma catecholamines which just exceed the threshold for cardiovascular and some metabolic effects. It should be noted that "not only are noradrenalin and adrenalin rapidly cleared but they also accelerate their own metabolic clearance" (Cryer, 1980; P438) so that only very heavy smoking would produce accumulations of adrenalin and measurable metabolic effects. For example, in order to demonstrate that cigarette smoking could produce an increase in plasma free fatty acids and so contribute to coronary heart disease, atherogenesis, and atherosclerosis, Kershbaum and Bellet (1968) resorted to giving three cigarettes in 20 mins ie chain smoking. The lack of realism of this dose can be seen from the fact that if sleeping took up eight hours and three hours were spent eating (generous assumptions) then a 40 a day smoker would have a cigarette every 20 mins. For average smokers the effect of nicotine on the adrenal medulla is no more than taking moderate exercise. The fatigue alleviation that would result from the metabolic changes will be discussed at the end of the next sub-section on nicotine and the adrenal cortex.

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3. Adrenal Cortex

The outer region of the adrenal gland is the adrenal cortex which contains zones of cells secreting hormones. The zona fasciculata and zona reticularies secrete the glucocorticoids of which the two most important, in humans, are cortisol and corticosterone. Unlike the adrenal medulla, release of hormones from the adrenal cortex into the circulation is controlled from the brain, via the release of adrenocorticotrophic hormone from the anterior pituitary, and not by the autonomic nervous system.

However the glucocorticoids like the catecholamines have marked metabolic effects but small or no haemodynamic action. They are essential for the mobilization of tissue proteins and for transferring the derived amino acids to the liver. The liver glycogen stores are limited and amino acids provide the major source of energy supply. In the liver, the glucocorticoids promote synthesis of enzymes that are used in gluconeogenesis. As well as conversion of amino acids to glucose, they also speed up extensive mobilization of depot lipid reserves, inhibit lipid synthesis and reduce glucose catabolism. Together these effects elevate plasma concentrations of glucose.

The glucocorticoids increase cardiac output and exert a "permissive action" on the cardiovascular effects of catecholamines in the sense that catecholamine vasoconstrictor responses are diminished when there are insufficient glucocorticoids. The two sets of hormones seem to be released in the same sort of circumstances, eg in response to stressors and when a person is concentrating. At the moment it is not clear what affects the different patterns of catecholamine and glucocorticoid release. Certainly, the two sets of hormones mobilize energy sources and prepare the person for action and reduce fatigue. The neural activation of the catecholamines ensures a rapid response, while the hormonal activation of the glucocorticoids results in a delayed, but more prolonged, action.

Adrenocortical secretion does increase after smoking although it does not seem to occur after only one cigarette. Kershbaum made habitual smokers chain smoke four unspecified cigarettes in thirty minutes and

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took plasma samples at 30 mins and 90 mins (Kershbaum, Pappajohn, Bellet, Hirabayashi and Shafiiha, 1968). The plasma corticosteroid levels were markedly elevated after 30 mins and still above baseline at 90 mins. In the commentary Kershbaum mentions that there was some release (range 22 to 46 per cent) when "Two cigarettes were smoked by each of several subjects" but no further details were given.

In a second study, habitual smokers were given 8 high nicotine (2.5 mg) cigarettes to smoke in a two hour session (equivalent to over 100 cigarettes per day; Winternitz and Quillen, 1977). According to the authors "A sharp rise in plasma cortisol occurred after two cigarettes which was maintained through the 2nd hour and fell slowly after the smoking period" (P396). In fact their graph (Figure 3) shows that cortisol levels are the same or lower after the second cigarette and it is after the third cigarette in half an hour that cortisol had increased. Only continual smoking increased the plasma cortisol concentration and maintained it above baseline levels for the two hours. The best conclusion that can be drawn from these studies is that high nicotine doses from exaggerated smoking rates can elevate plasma glucocorticoids. An alternative interpretation is that the rapid smoking was aversive and stressed the subjects. Incidentally, the US Surgeon General's Report (1979) only cites the preliminary study of Winternitz and Quillen in which non-smokers smoked six cigarettes in two hours, were sick and had increased adrenocorticotrophic hormone levels.

If we accept the most charitable interpretation that smoking produces some release of glucocorticoids from the adrenal cortex then these hormones, combined with the catecholamine release, will make available energy sources for use by the brain and the rest of the body. In this way smoking would alleviate mental and muscle fatigue. Studies of carbohydrate and lipid use in physical work of different intensities have found that during exhausting work there was a depletion of carbohydrates, but subjective symptoms of fatigue disappeared within 15 min of ingesting glucose which increased the blood-sugar levels again (Christensen and Hansen, 1939). The central nervous sytem has low reserves of glucose and depends on blood carbohydrate for its supply of energy. In man about 60 per cent of the liver glucose output supplies brain metabolism, and so exhaustion

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Figure 3

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seems to be as much a central nervous phenomenon as is lack of sugar for muscles peripherally (Åstrand and Rodahl, 1970).

It has been suggested that the elevation of blood glucose could be responsible for the satisfaction derived from smoking because glucose would activate the reward pathways in the hypothalamus (Surgeon General, 1979). Carruthers (1975) used oxprenolol to block the responses to catecholamines release by smoking ie free fatty acid mobilization, blood pressure and heart rate increases. The subjective reports indicated no effect on satisfaction after smoking, which rules out the involvement of blood glucose (and blood pressure and heart rate increase) in satisfaction. It seems more likely that satisfaction is the outcome of the changes in the central nervous system.

4. Central Nervous System

The first evidence for "nicotinic" receptors in the central nervous system came from studies of the Renshaw cell in the spinal cord (Eccles, Eccles and Fatt, 1956). It was shown that when either 200 µg of acetylcholine or 1 µg of nicotine were injected close to the cell an action potential was produced. The response to nicotine was the same as that to acetylcholine but more prolonged because, unlike acetylcholine, it was not inactivated by acetylcholinesterase. When acetylcholinesterase was inhibited by physostigmine, acetylcholine produced a much larger response, but the response to nicotine was unchanged, which showed that nicotine's effect was directly on the post-synaptic receptors of the Renshaw cell and not via the release of acetylcholine. Nicotine antagonists reduced the response to both acetylcholine and nicotine, also indicating that nicotine was acting directly on cholinergic synapses. Many studies have now shown that there are nicotinic receptors on this cell although there seem to be muscarinic and even mixed synapses as well (Curtis and Ryall, 1966).

Studies with iontophoretically applied acetylcholine have revealed that this transmitter excites neurones in many regions of the brain (Phillis, 1970) including the medullary and mesencephalic reticular

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formation, lateral and medial geniculate, caudate nucleus, ventrobasal complex of the thalamus, hippocampus, cerebellum, inferior colliculus and the Betz cells of the deep pyramidal layer of the cerebral cortex. Cortical cells and caudate nucleus cells clearly have muscarinic receptors which were relatively insensitive to nicotine while acetylcholine receptors in the geniculate nuclei, ventrobasal thalamus, hippocampus and reticular formation nuclei were sensitive to both nicotinic and muscarinic drugs. Cholinergic inhibitory neurones, with mixed nicotine and muscarinic receptors, have been found at the cortex in layers II, III and IV of the primary sensorimotor auditory and visual areas.

In spite of the clear evidence that the cholinergic neurones at the cortex are predominantly muscarinic, "smoking" doses of nicotine (eg 20 µg/kg in the cat) produce excitation of cortical cells (Knapp and Domino, 1962; Kawamura and Domino, 1969; Armitage, Hall and Sellers, 1969) and release of acetylcholine at the cortex (Armitage et al, 1969). In the study of Kawamura and Domino (1969) blood pressure was kept constant with drugs, so that the effect was not due to vascular changes.

Cortical acetylcholine release and cortical excitation can be produced by stimulation of the mesencephalic reticular formation and this phenomenon can be reduced in one hemisphere by unilateral destruction of this region ipsilaterally (Celesia and Jasper, 1966). In a neuropharmacological analysis of the effects of "smoking" doses of nicotine after destruction of the midbrain (Domino, 1967; Kawamura and Domino, 1969), 20 µg/kg of nicotine produced cortical desynchronization and hippocampal synchronization in cats with a caudal midbrain transection at the junction of the pons in exactly the same way as intact animals given nicotine. After bilateral lesions in the tegmental region of the midbrain, nicotine in doses up to five times the 20 µg/kg "smoking" dose did not activate the cortex. Clearly, nicotine's action on the cortex depends on an intact tegmental region. The ventral tegmental region of the mesencephalic reticular formation is the origin of a cholinergic pathway which projects to the cortex (Shute and Lewis, 1967) and there is good evidence that it terminates on the pyramidal Betz cells at the sensory cortex and produces electrocortical arousal (see review by Warburton, 1981).

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The most parsimonious conclusion is that "smoking" doses of nicotine ascend in the carotid artery and excite nicotinic receptors on the tegmental-neocortical cholinergic pathway in the midbrain. Nicotine does not act directly on the cortex but the outcome of activation of the pathway at the midbrain is release of acetylcholine at the cortex and cortical desynchronization.

C. Nicotine and Human Psychophysiology

In this section we will consider the action of nicotine on the human cortex in the context of psychophysiology, the correlation of neurophysiological events with human behaviour. The first part will consider the effects of nicotine on cortical desynchronization, the second part will outline nicotine's action on the contingent negative variation while the third part will discuss event related potentials. The methodology of this research has been critically reviewed by Edwards (submitted for publication).

1. Cortical Desynchronization

Electrocortical activity is recorded by scalp electrodes which enable the measurement of the composite activity of cortical cells through the skull and scalp. When the firing of cells is synchronized, as they are during some periods of sleep, the electroencephalogram (EEG) shows low frequency (½ - 5 Hz), large amplitude (ie high voltage) waves (delta waves). When a person wakes and becomes alert, the waves decrease in amplitude and increase in frequency through theta waves (4 - 7 Hz), alpha waves (8-12 Hz) to beta waves (13 - 50 Hz). A high proportion of beta activity, cortical desynchronization, is correlated with a state of full alertness and concentration in the person while a high proportion of alpha activity is correlated with relaxed wakefulness.

Many human studies have shown that smoking increases the amount of cortical desynchronization in the form of an upward shift in dominant alpha frequency ie more 10 - 12 Hz (eg Hauser, Schwartz, Roth and Bickford, 1958), less total alpha activity and more beta activity (eg Knott, 1979; Murphree, 1979). Thus these human studies show that smoking

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produces cortical desynchronization just as nicotine does in animal studies. In a study correlating performance with electrocortical activity, Warburton and Wesnes (1979) found that both cigarettes and nicotine-tablets increased the dominant alpha frequency (11.5 - 13.5 Hz) and beta activity (13.5 - 20 Hz).

In the same study, performance on a task involving concentration was improved by the same treatments. Many other studies at Reading University have confirmed that smoking and nicotine tablets, given to smokers and non-smokers, improve performance in tasks requiring sustained concentration (eg Wesnes and Warburton, 1978; 1982). In none of these studies were there differences in the effect of nicotine on performance in smokers and non-smokers. Therefore, it it significant that Murphree (1979) was unable to find any differences in the cortical desynchronization of smokers, who smoked at least 10 cigarettes per day, and non-smokers produced by an intravenous nicotine dose of 1.86 mg, a "smoking" dose. In other words, the smokers responded in the same way as non-smokers and there was no evidence of tolerance to nicotine's effect on electrocortical activity. These results make sense because of the molecular similarity of nicotine and acetylcholine. The brain cannot become tolerant to its own transmitters, and as nicotine is similar enough to acetylcholine, tolerance does not develop to nicotine either. This lack of tolerance to nicotine explains why smokers do not increase their consumption of cigarettes over the years (apart from compensating for any decrease in average nicotine - see page 90).

In concluding this illustrative review of nicotine's action on cortical desynchronization, it must be emphasised that the shifts produced by nicotine are within normal limits ie they are indistinguishable from those that occur when a person is concentrating hard. There is certainly no evidence of the EEG abnormalities that occur with other psychostimulants eg amphetamine. Smokers claim that they smoke to help them think and concentrate and nicotine's action on cortical desynchronization produces the neural state for satisfying this need. Evidence that smokers can control their nicotine intake to produce a specific brain state has come from contingent negative variation studies.

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2. Contingent Negative Variation

The contingent negative variation (CNV) appears as a slow negative shift of cortical potential during the period between a warning signal and an imperative stimulus which requires a motor response or a decision. Thus, the CNV represents a cortical change associated with planned action before a response to a sequence of two or more events. Significant correlations have been reported between CNV amplitude and measures said to represent selective attention, arousal, motivation, anticipated energy output, conation, orientation, expectancy, and preparation for action, but selective attention or concentration is the most commonly used concept.

Experiments on the CNV and smoking (Ashton, Millman, Telford and Thompson, 1974; 1976; Ashton, Marsh, Millman, Rawlins, Telford and Thompson, 1978; Comer, Binnie, Burnett, Darby and Thornton, 1975; Binnie and Comer, 1978) have correlated CNV with subjective reports of feeling either "relaxed" or "stimulated" following smoking. Ashton collected personality information and estimated (by analysis of the cigarette butt) the amount of nicotine taken into each subject's mouth. After smoking, CNV amplitude increased in seven subjects, decreased in eleven and showed a biphasic response in four (Ashton et al, 1974). "Smoking" an unlit cigarette by three other subjects resulted in no CNV amplitude changes. Repetition of the smoking sessions for eleven of the subjects, on a different occasion, produced the same directional changes in the CNV in these individuals.

Ashton and her co-workers argue that the origin of the CNV is in the ascending reticular activating system and probably the limbic system and they assume that there is a positive relationship between CNV magnitude, activity in these systems and the individual's level of stimulation. Data from drug studies support these assumptions: CNV magnitude increased after doses of the psychostimulant caffeine and CNV magnitude decreased following oral doses of the sedative, diazepam (Valium) (Ashton et al, 1974; 1978).

Ashton et al related individual differences in CNV to personality and smoking behaviour. By dividing their group at the extraversion mean they

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found that the eight more extraverted subjects took a smaller oral dose of nicotine per minute and showed a mean increase in CNV magnitude after smoking, while the eight more introverted subjects showed the reverse. They attempted to analyse subjective experiences of smoking but these did not provide clear data. However, there was some evidence from subjects that self-report of a "sedative" effect of smoking was associated with a fall in CNV whereas "stimulation" was associated with a rise in CNV.

Ashton and her co-workers (1978) also examined the effects of intravenous nicotine. They gave discrete pulses of nicotine to provide a total dose similar to that obtained by a smoker who inhales a cigarette delivering 1 - 2 mg of nicotine. The same direction of change in CNV occurred in individuals who took part in both smoking and nicotine sessions. Saline injections produced no significant changes. As a further refinement, Ashton et al (1978) examined the question of whether the CNV changes are dependent on the dose of nicotine or, alternatively, on the characteristics of the smoker and, therefore, largely independent of dose. Over a range of doses, from 12.5 - 800 µg, there was an inverted U relation between CNV magnitude and dose; with lower doses (12.5 - 50 µg) the CNV increased as the dose increased, but with further increases (100 - 800 µg) there was a progressive reduction in CNV magnitude. This pattern was evident for all seven subjects although the precise dose-response relation was not the same for each of them.

In summary, smoking and nicotine produced similar changes in the CNV in the same person. Nicotine increased or decreased the CNV amplitude depending on the dose and subjects seemed to control their smoking behaviour in order to obtain a particular dose. These findings were combined by Ashton to give the hypothesis that individuals adjust their smoking behaviour to the amount of nicotine for a particular brain state and so control their psychological state. The desired state will depend on the outcome of interaction between the individual and the situation and, by adjusting the nicotine dose, the same individual may use a cigarette to provide a stimulant effect on one occasion and a depressant effect on another.

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3. Event-Related Potentials (ERP)

Event-Related Potentials, sometimes known as Averaged Evoked Potentials, are the complex electrical changes recorded at the same time as a physical or mental event and represent the activity of groups of neurones in the brain. The obvious advantage of the ERP technique is that it provides a continuous record of events occurring in the brain during psychological processes. The problem with recording the electrical activity from the scalp associated with a single event is that it is too small to detect against the background of cortical desynchronization and so "signal averaging" techniques are employed to distinguish ERP's from the obscuring background activity. If the ERP is the same with every event then it will become more and more recognizable against the random EEG noise during the averaging process.

With repetitive stimulation, the post-stimulus waveform between 0 to 250 msec consists of components which are essentially constant in amplitude, latency and scalp site distribution for a given stimulus. These exogenous components occur whether the subjects attend or not, are awake or asleep, aroused or relaxed. Of particular interest are the so-called endogenous components which are emitted or elicited, often in the absence of stimulation, and whose characteristics are partially independent of the physical characteristics of stimuli. The major endogenous component which has been identified is the P_3 or P300 whose latency ranges from 275 - 600 msec. The P300 is particularly sensitive to the subject's prior experience, intentions and decisions and varies according to the task requirements and experimental instructions.

A recent experiment (Edwards, Wesnes, Warburton and Gale, in preparation) enabled an analysis to be made of the effects of smoking on the ERPs to correct target detections in a rapid information processing task. In this test subjects were instructed to detect and respond to triplets of three odd or even digits in a sequence of single numbers that were presented on a TV screen at the rate of 100 per minute. Good performance depended on subjects maintaining their concentration throughout the 20 minute session. Preliminary analysis has shown that smoking produced large decreases in the latency of P300 (20-30 msec decrease) and small decreases in the amplitude of P300. A reduction in P300

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latency is interpreted as a decrease in the time taken to evaluate or categorise a stimulus while a decrease in P300 amplitude is thought to mean that the subject is using less neural "resources" in processing. For example, when the probability of a signal is high then the amplitude is smaller than when the stimulus is novel because the information needs less analysis by the brain. Analysis of the performance showed that smoking increased the targets detected and decreased the reaction time (see sub-section IV D). This improvement of performance fits neatly with the P300 changes which are indicative of more efficient neural processing of the stimulus.

D. Psychopharmacology of Nicotine

In this section evidence will be presented on the implications for human behaviour of the neural states that are induced by nicotine. As we have seen, nicotine stimulates and produces increased neural efficiency. There is also evidence that nicotine can produce neural changes that have been interpreted as a sedation effect. Questionnaire surveys (eg McKennell, 1970; Thomas, 1973; Russell, Peto and Patel, 1974) have shown that a desire for stimulation and a desire for sedation are two of the major motives for smoking for a majority of smokers. Accordingly, this section will concentrate on the evidence for more efficient performance after nicotine and the effects of nicotine on mood states.

1. Performance

There are many possible tests of human performance which are sensitive to drugs, but a major problem is interpreting the data in terms of the psychological processes which are modified. These include (1) sensation (the input of information); (2) attention (selection of information); (3) processing of information; (4) learning and memory (storage of information); and (5) motor output (the response). Ideally, experiments are designed to study one process by minimising the influence of others on performance.

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The earliest of the acceptable studies was done by Hull (1924). He used a within subject design and compared the effects on performance of tobacco smoke from a pipe and of moistened hot air. He measured several physiological variables and increases in heart rate indicated that subjects were absorbing nicotine from the tobacco smoke so it is reasonable to attribute the effects of smoking to nicotine. Nicotine improved reaction time and increased the speed but not accuracy of mental addition but impaired rote learning and memory span. In general, experienced smokers were more affected than non-smokers, suggesting that they had absorbed more nicotine from the tobacco smoke, probably by inhalation. This evidence suggests that nicotine is increasing information processing speed but interfering with information storage. However, it is not possible to rule out the explanation that the faster reaction was due to improved attention to the stimulus or the possibility that the impaired information storage was due to interference with the sensory input.

a. Sensation

There is little evidence from subjective reports of smokers that smoking has any effect on the ability to receive information from the environment, except perhaps for possible blunting of taste and smell. So it is not surprising that there is no confirmed evidence that nicotine significantly facilitates or impairs this process, although some research suggests that smoking raises sensory thresholds slightly ie the smokers are less sensitive to stimuli (Larson, Haag and Silvette, 1961). However, there are also reports that smoking doses of carbon monoxide increase brightness thresholds by about 3 per cent (Halperin, McFarland, Niven and Roughton, 1959) which would explain the small changes in threshold that were produced by smokers. Even for taste the evidence for changes after smoking are not clear cut. Pangborn and Trabue (1973) reviewed 16 experimental studies between 1937 and 1970 of which 11 reported impaired taste and/or smell with heavy smoking, and 5 which found no difference or negligible changes in sensitivity. The effects of nicotine alone on sensory thresholds have not been studied.

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A second test, which has been used to assess the effects of smoking on sensation, is the critical flicker fusion test. Briefly, this task requires the subject to discriminate between intermittent photic stimulation which either appears to flicker or appears to be a steady light. The dependent variable is the frequency of flashes at which the change in appearance occurs. A rise in threshold could indicate better sensory processing. A comparison of smokers deprived since the previous night with deprived smokers, who were allowed to smoke a cigarette before testing, showed that smoking increased the threshold slightly (Larson, Finnegan and Haag, 1950). A later study tested a small oral dose of 0.1 mg of nicotine in the form of tobacco powder (Warwick and Eysenck, 1963) and found an elevation of the fusion threshold by about seven per cent. The importance of these changes is difficult to interpret because the finding cannot be related to real life situations. It is believed that the mechanism for critical flicker fusion is at the cortex because alternate flashes to both eyes will produce fusion and so Warwick and Eysenck claim that it is a measure of cortical reactivity rather than sensory processing. In the next section we will be considering the process of attention which is also related to cortical arousal.

In summary, there is little direct or indirect evidence that nicotine improves or impairs sensation to an extent for which it is of practical significance.

b. Attention

Subjective reports from smoking motive questionnaires (eg Russell, Peto and Patel, 1974) indicate clearly that smokers believe that smoking helps them to think and to concentrate. The first piece of experimental evidence to suggest that this experience of enhanced concentration was due to nicotine came from a complex vigilance study by Tarrière and Hartemann (1964) in which subjects performed a main guiding task with a subsidiary visual monitoring task. They counted correct detections of peripheral signals, false detections and guidance errors and said that they measured plasma nicotine and several physiological variables including heart rate and EEG. The test

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groups were non-smokers, smokers deprived for 20 hours and smokers allowed to smoke unspecified cigarettes whenever they wished. Unfortunately they do not give the plasma nicotine levels and their section and graph of "level of nicotine" refers to carbon monoxide. No EEG data are given but an elevation of heart rate, after smoking, indicates some nicotine absorption. Vigilance performance, which was measured in terms of percent omissions, declined in non-smokers and deprived smokers during the 150 minute test but nicotine maintained detection performance throughout the session. No other behavioural data were given on detection errors or guidance errors, presumably because they did not change, but in view of the mistakes in the paper we cannot be certain about this lack of effect. If performance detection had been maintained at the expense of guidance then we could not conclude that concentration was enhanced.

Results which were consistent with Tarrière and Bartmann's study were outlined in a report of smoking and simulated driving (Heimstra, Bancroft and DeKock, 1967). The study will only be mentioned briefly because no physiological measures were taken so the effect of smoking on performance cannot be attributed to nicotine. Heimstra et al studied the effects of smoking and smoking deprivation on brake light vigilance, meter vigilance, steering and brake pedal reaction time. Three groups were used: non-smokers, smokers who were deprived for the six hour test and smokers who could smoke as much as they wished. The consequences of smoking were better performance in comparison with deprived smokers; this effect was manifested as prevention of performance deterioration rather than a performance improvement above control levels.

Frankenhaeuser and her colleagues (Frankenhaeuser, Myrsten, Post and Johansson, 1971) also found that smoking during a prolonged reaction time task enabled subjects to maintain their performance. All subjects were deprived of cigarettes for 10 hours prior to testing. Half of them remained deprived throughout the test while the other half were allowed a 1.4 mg nicotine cigarette after 20 mins, 40 mins and 60 mins of testing. Heart rate increases confirmed that nicotine had been absorbed and the urinary adrenalin levels of the smokers were higher.

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The reaction times for the deprived smokers increased during the course of the 80 minute session while smoking maintained the reaction time. As a group, the smokers also reported that they felt more alert and more relaxed when smoking.

Essentially, the same findings were obtained when the study was repeated using either a similar prolonged test - a low arousal test, or a similar test but with the added stress of two other tasks to be performed at the same time - a high arousal test (Myrsten, Post, Frankenhaeuser and Johansson, 1972, Myrsten, Andersson, Frankenhaeuser and Mardh, 1972). The smokers were sub-divided, on the basis of a questionnaire, into smokers who smoked more often in low arousal situations and those who smoked more often in high arousal situations. Reaction times were better for low arousal smokers who smoked during the low arousal test than when they were deprived but smoking was not beneficial during the high arousal test. The opposite finding was obtained for the high arousal smokers; they only improved with nicotine in the high arousal test. These two studies were the first to reveal that performance was the outcome of a smoking x individual x situation interaction.

In studies at Reading University (Wesnes and Warburton, 1978) smokers deprived for 12 hours and non-smokers were tested on a visual vigilance task which consisted of detecting brief pauses in the minute hand of a clock. Detection performance declined over the 80 minute test in all subjects who did not smoke but deprived smokers who smoked a 1.4 mg cigarette at 20 mins, 40 mins and 60 mins (as in the Frankenhaeuser studies) showed no decrement in detection performance. This experiment revealed that cigarettes helped smokers to maintain better detection performance than either deprived smokers or non-smokers. The two non-smoking groups did not differ significantly so there was no evidence that cigarette deprivation was an important factor. Evidence that this effect was due to nicotine came from a second study with this task using 0, 1 and 2 mg nicotine on alkaline tablets held in the mouth, which enabled buccal absorption of nicotine (Russell and Wesnes, unpublished). The tablets were given to smokers after the same 20 minute intervals as before, in a repeated measure design. During

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the first 20 minutes, performance in the three conditions was matched to give a baseline and a comparison of the three conditions showed a clear dose related improvement after the first and second tablets at 20 mins and 40 mins. However, after the third tablet at 60 mins, performance was worse in the 2 mg group than the 1 mg group. This difference was probably due to the toxic effects of the cumulative dose of 6 mg of nicotine in an hour.

In a third study, cigarettes yielding 0.31, 0.71, and 1.65 mg of nicotine were compared using a version of the vigilance task, with well defined detection intervals and the same experimental design as before. The cigarette butts were analysed to estimate the amount of nicotine which was generated by the smoker. The best group performance, during the first 20 minutes after a cigarette, was obtained after smoking the 0.71 mg nicotine cigarette rather than after smoking the 0.31 mg nicotine cigarette. However, the butt analyses showed that smokers obtained estimated mouth levels of 0.63 mg of nicotine from the 0.31 mg nicotine cigarette, 1.3 mg nicotine from the 0.71 mg nicotine cigarette and 1.5 mg nicotine from the 1.65 mg nicotine cigarette giving evidence of titration. Analyses of individual differences gave clear evidence that subjects who scored high on neuroticism smoked harder at the beginning of the session than low neuroticism subjects while there was some evidence that subjects who scored high on extraversion smoked more intensely at the end of the session than the more introverted subjects. The performance data showed that smoking produced most improvement in subjects with high neuroticism scores. An individual difference analysis of the nicotine tablet study, that was described above, gave similar evidence. Once again, these studies suggest that subjects had a need for nicotine to help them perform within the experimental situation. This need determined the smoking behaviour and performance was the outcome of the interaction of the situation, the individual and smoking.

As well as examining the effects of nicotine and smoking in a long boring task we have also examined sustained attention in a shorter 20 minute rapid information processing test. In a set of eight studies (see Wesnes and Warburton, 1978 and in press) we have tested

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cigarettes of different nicotine deliveries ranging from 0 mg (herbal cigarette) to 2 mg as well as nicotine tablets. The test consisted of a random series of digits, presented individually on a TV screen, at a rate of 100 per min and subjects were asked to respond if they saw a sequence of three odd or three even digits. Eight of these triplets were presented every 10 minutes. Each subject was tested for 10 minutes before a further 20 minutes after a cigarette or tablet. Performance was compared with both the pre-drug baseline and the no smoking, herbal cigarette or placebo tablet conditions. Rather than discuss each individual study only the overall pattern of the findings will be presented. During the three control conditions performance declined over the 20 minute session, in exactly the same way for herbal cigarettes and no smoking, showing that the smoking act itself had no influence on performance in terms of correct detections.

Smoking not only improved performance relative to not smoking but produced an absolute enhancement relative to the pre-nicotine baseline in the first 10 minutes. The absolute enhancement was 11 - 14.5 per cent better than baseline and occurred in 68 - 75.5 per cent of the subjects for each cigarette in each study. In general, a greater improvement was seen after high delivery cigarettes than low delivery products but there was overlap between cigarettes of similar delivery probably due to nicotine titration by the subjects. Conclusive evidence that the better detection performance was due to nicotine came from a study with non smokers using alkaline tablets containing nicotine (Wesnes and Warburton, in press). Doses of 0.5, 1.0 and 1.5 mg of nicotine significatnly reduced the decrement of detection that occurred in the placebo condition and the 1.5 mg dose produced a significant absolute improvement relative to the pre-drug baseline. In this task the stimuli were well above threshold, the memory component was small and the motor response was a simple button press so it can be concluded that nicotine was enhancing either the attentional process, information processing, or both processes.

Support for enhancement of the attentional process comes from a study of nicotine tablets and the Stroop effect. In the Stroop test, subjects name the colours of a set of colour spots and then they are

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presented with a set of colour words printed in another colour. There is a difference between the time taken to read the two sets, known as the Stroop effect, because of the distractions produced by the incongruity between print colour and colour word. Nicotine doses of 1 mg and 2 mg reduced the magnitude of the Stroop effect in both smokers and non-smokers and there was no difference in the size of the effect in smokers and non-smokers. This evidence argues strongly for the hypothesis that nicotine helps a subject to ignore distracting information and concentrate on relevant information.

In summary, this body of data supports the subjective experience of smokers that smoking helps them to concentrate. Correlative physiological and biochemical data together with the nicotine tablet studies indicate that nicotine in cigarette smoke is the agent responsible for this effect. As we have seen, nicotine increases electrocortical arousal and so this work fits neatly with research demonstrating that drugs which modify electrocortical arousal change attentional performance; increases in electrocortical arousal enhance attentional filtering while decreases impair this process (see review Warburton, 1981). In this way nicotine enables subjects to sustain their concentration and filter out distractions.

c. Information Processing

Some evidence for more efficient processing with nicotine came from the early study of Hull (1924) who demonstrated that nicotine, from pipe smoke, decreased reaction time and improved addition speed. This finding was supported by a study of cigarette smoking and simple reaction time (Fisher, 1927). It could be argued that, in simple reaction time studies where subjects only have to decide if a light is present, the information processing component is small, but faster addition without loss of accuracy would seem to support the hypothesis of greater processing efficiency.

The studies of smoking and nicotine tablets and rapid information processing (Wesnes and Warburton, in press) provide unequivocal evidence for more efficient processing when using cigarettes or tablets with nicotine. As we have seen, both cigarette smoking and nicotine tablets

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improved detection of the triplets of three odd or three even digits in a string of single numbers flashed on a computer screen. The reaction times of these detections were also recorded and it was found that nicotine from cigarettes and tablets reduced reaction time. The reaction time improvement was around seven per cent and between 65 and 77 per cent of the subjects were improved depending on the nicotine delivery of the cigarette. This finding is very important because it shows that there is no trade-off between speed and accuracy and there was an overall improvement in processing efficiency.

This behavioural data fits neatly with the study of Edwards et al (in press) which showed that smoking decreased the latency and amplitude of the P300 wave of the event related potentials in the rapid information processing task that was referred to previously in Sub-section IV C3. In this study the behavioural data also showed faster reaction time and improved detection of the odd and even triplets of digits. Thus both behavioural and electrocortical measures indicate that nicotine is enabling more efficient processing of information in the brain.

In summary, the evidence from this section and the last section are consistent in showing that nicotine by its action at the cortex of the smoker produces better information selection and faster, more accurate evaluation of that information.

d. Learning and Memory

The effects of nicotine on learning have been investigated most extensively by Karin Andersson. The first study, (Andersson and Post, 1974) compared the effect of nicotine-free cigarettes and nicotine cigarettes on learning a nonsense syllable list on light smokers (less than five per day) who were deprived for 12 hours prior to the testing. On the first test day subjects always smoked a 2.1 mg nicotine cigarette and on the second day subjects were given a nicotine-free cigarette. Significant increases in heart rate showed that the subjects were absorbing nicotine from the nicotine cigarettes. The first cigarette was given after the first ten trials of learning the list of nonsense syllables and a second cigarette, of the same

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kind, was given after 20 trials; trials were given every two minutes. The learning curves were identical for the two conditions prior to smoking, but after smoking, the number of correct syllables decreased when the subjects had the nicotine cigarette and remained below the performance in the nicotine-free condition although the learning curves were parallel. After the second nicotine cigarette, the number of syllables correctly repeated increased significantly and reached the same level of acquisition performance as in the nicotine-free cigarette condition. Thus, relative to the previous performance, nicotine had improved recall of the syllables. These data give no evidence of nicotine impairing learning because the learning curves are parallel after the nicotine cigarette. It was as if the information stored in the non-nicotine state was less available in the drug state, a phenomenon known as state-dependent learning. We will return to tests of this possibility later.

In a related study using nonsense syllables (Andersson, 1975 a) a similar learning procedure was used in which subjects smoked either a high nicotine cigarette (2.1 mg) or did not smoke after the tenth trial. Heart rate changes indicated nicotine absorption in the smoking condition. After trial 20 there was an interval of either 8 minutes or 45 minutes when subjects were given a jigsaw puzzle to solve to prevent rehearsal. Then, a single recall trial was given 26 or 65 minutes after smoking. Performance on trials 1-10 were the same for the smoking and no smoking conditions, nicotine decreased recall on trials 11-20 although did not affect the rate of acquisition. After 8 minutes there was poorer recall in the nicotine condition ($p<0.05$), while after the 45 minute interval there was some evidence ($p<0.10$) that recall was better after nicotine than no nicotine. The slight superiority of the nicotine group shows that the decrement in performance, after trial 10, could not be due to an impairment of information input and storage by nicotine and there could even have been an improvement of one of these processes. From the earlier discussion we can hypothesise that this effect could have been due to more efficient input of information after nicotine, and the impairment after trial 10 due to a change of state. The difficulty of interpreting the effects of nicotine in this study,

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and in the last one is that learning and recall are occurring over a 20 minute period while plasma and brain levels of nicotine fall by a half.

In a third study, relating nicotine and recognition memory, Andersson (1975 b) tested smokers on recognition of previously presented numbers. A set of the numbers 1-25 were randomly presented to the subjects who were required to respond if they remembered that they had seen a number before. Three sets of numbers were given so that the task became more complex as the test proceeded. There was a high nicotine cigarette (2.3 mg), a low nicotine cigarette (0.37 mg) and a no smoking condition. Heart rate increases indicated absorption of nicotine from the cigarettes. No statistically signficiant differences ($p<0.1$) were obtained but on the first number, set recall was better in the no smoking condition than in the low nicotine condition, and recall was worst in the high nicotine condition. On the second and third number sets the order was reversed ie better recognition after smoking. These trends on the last two sets can be interpreted in terms of nicotine improving information processing by enabling the subjects to select the 'relevant' information (the digits of the present set) from the irrelevant (the digits presented in the previous set or sets).

The final study of Andersson (Andersson and Hockey, 1977) used a memory test that consisted of relevant and irrelevant information which enables this selectional interpretation to be examined further. A list of eight Swedish adjectives were presented, one at a time, in one of the four corners of a screen and the subjects were told that they would have to write down the words in presentation order ie the words and their order were relevant and by implication location was irrelevant. Two groups of smokers, deprived of cigarettes for 12 hours, received either a high nicotine cigarette (2.3 mg) or remained deprived. There were no differences between the nicotine and no nicotine groups for percentage of words that were recalled in the correct order, or for the percentage of words that were recalled correctly regardless of word order. This finding contradicts Andersson's previous evidence on recall. The most interesting

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finding was the decreased amount of irrelevant information recalled with nicotine; positions on the screen were recalled significantly less well with a group recall score of 30.2 per cent, which is only just above the chance level of 25 per cent. In a second test, in which subjects were required to remember words, word order and screen position, the groups did not differ significantly in their recall although there was a trend for location to be recalled better after nicotine (62.2 per cent) than when deprived (55.3 per cent). These data on recall also contradict the previous findings. This study suggests that nicotine can enable more limited and selective processing of information but it should be noted that the effect only occurs when the information is thought by the subjects to be incidental and not when the subjects were asked to remember it ie nicotine is not acting on a passive system.

In the earlier discussion the possibility of nicotine producing state dependent learning in human subjects was mentioned and numerous animal studies have given evidence of state dependency with cholinergic drugs (see review in Warburton, 1977). In a state dependent design one group of subjects learns after a drug dose while a second group learns after a placebo or no drug. For the recall test both groups are divided in two, one half of each group are tested with the drug of learning and half are switched to the other condition. If the recall scores are better for those groups which had the same drug state, then state dependent learning is said to have occurred. This state dependency hypothesis with nicotine has been investigated in several studies.

In the first published study (Houston, Schneider and Jarvik, 1978) 23 heavy smokers, deprived of cigarettes for three hours, read a list of words and were then given a free recall test prior to smoking in order to match the groups for learning ability. One group smoked a 1.5 mg nicotine cigarette and the other group smoked a non-nicotine cigarette. Smoking behaviour was controlled by asking the subjects to puff 12 times at thirty second intervals and to inhale and hold the smoke in their lungs for five seconds before exhaling. Although puff volume, puff duration and depth of inhalation were not controlled,

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the procedure would make it more likely that a relatively uniform amount of nicotine was absorbed by the group. Controlling the dose in this way makes the study pharmacologically sophisticated but it may be nonsensical from the point of view of the smokers, who would prefer to titrate for their own dose.

After this controlled smoking procedure, the subjects were given three successive lists with free recall tests after each one. The immediate recall scores showed that the nicotine group had significantly poorer recall than the placebo group although their pre-smoking scores were not different. These findings match those of Andersson and Post (1974) and Andersson (1975 a). Forty eight hours later, eight of the subjects from each condition returned for retesting and were sub-divided giving four groups of four subjects. They smoked either a nicotine or a non-nicotine cigarette as before, followed by another free recall test of all the lists. Once again the recall scores of the subjects, who smoked a nicotine cigarette at the time of learning, were significantly worse than those who smoked a non-nicotine cigarette which was not consistent with the findings of Andersson and Post (1974) and Andersson (1975 a). No evidence of state dependent learning was obtained, ie the group receiving a nicotine cigarette or a non-nicotine cigarette on both learning and recall did not have better scores than subjects who switched their cigarettes. However, with such small groups it is not surprising that no differences were found.

In contrast with the last study, two more studies have found positive evidence for state dependent learning with nicotine (Warburton, Wesnes and Shergold, 1982). The first experiment used the state dependent design to test nicotine's effect on recognition memory. Forty smokers, who were deprived of cigarettes for 10 hours, were given a 1.4 mg nicotine cigarette or allowed to relax immediately before serial presentation of a set of 30 Chinese radicals. After presentation, the subjects were allowed to read for one hour until the recognition recall test when they were divided into four groups - no smoking prior to learning and recall; no smoking prior to learning but a cigarette prior to recall; a cigarette prior to learning and recall; and a cigarette prior to learning but none prior to recall.

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Subjects who received nicotine prior to learning had significantly better recognition scores than the subjects who did not smoke in the first part of the experiment. There was no effect of nicotine on recall performance. A significant interaction term indicated that changing drug state interfered with recognition.

A more elaborate study examined the effect of a controlled dose of nicotine on short-term and long-term recall, within the framework of a state dependent design. Subjects, who were smokers deprived of cigarettes for ten hours, held a 1.5 mg alkaline nicotine tablet (pH 9) or a placebo tablet in their mouth for five minutes to allow nicotine absorption, tablets were then swallowed. Buccal and gastric absorption would be expected because of the alkaline tablet and this combination produces plasma levels of nicotine which remain stable for 30 mins (Russell and Wesnes, unpublished). After the tablet, the subjects listened to a list of 38 words and then did successive subtraction of seventeen from a larger number for one minute to prevent rehearsal. A free recall test was given for 10 minutes and then the subjects were allowed to leave the test room but were told that they would be called in 1 hour for a second, unspecified test. They were instructed not to smoke in this interval. During the hour they worked and were then recalled, given either nicotine or placebo tablets, depending on their group, and asked to recall as many of the words as they could in another 10 minutes free recall test.

The short term recall data revealed a very significant superiority of the nicotine group over the placebo group. Long term recall was also significantly better when subjects had taken nicotine prior to learning but not when taken prior to recall. The very significant interaction term again gave evidence for a state dependent effect of nicotine and showed that nicotine was facilitating the input of information to storage but had no direct effect on storage or retrieval. These findings are consistent with previous results which showed that nicotine facilitated information processing. However, the state dependency effect, for which there was some evidence in the studies of Andersson and Post (1974) and Andersson (1975 a), resulted in a poorer recall when subjects either learning with nicotine but recalled without nicotine or vice versa. In view of the previous discussion of

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nicotine's effects on information processing, a state dependent effect is not surprising because of the differences in the selection and processing of information due to nicotine increasing electrocortical arousal. A large body of literature has demonstrated that recall is better when the learning and recall situations are identical.

In conclusion, these studies show that in some circumstances nicotine can enhance the storage of information, probably because of more efficient input of information, but recall may be less efficient if the person is tested without nicotine. For habitual smokers this impairment would only be likely if they were deprived of cigarettes. It should be emphasised once again that this conclusion agrees with animal studies of learning with nicotine and with studies of cholinergic drugs and learning in general.

e. Motor Output

There is no evidence of gross changes in motor output after smoking doses of nicotine or nicotine tablets and the only change is a reliable increase in hand tremor after smoking (Larson et al, 1950). Although nicotine does act directly on neuromuscular junctions, (see sub-section IV B1) the tremor seems to be due to an effect on the central nervous system as well, perhaps at the level of the motor regions of the mesencephalic reticular formation. This fine tremor seems to have no practical significance except that it can be used as a marker for nicotine absorption.

f. Conclusions

Smokers report that they smoke to help them think and concentrate and the experimental evidence supports this rationale. Smoking and nicotine produce better selection of information from the environment and faster processing of that information which is reflected in improved attention and learning. There is some evidence that the improved learning by nicotine does not always transfer completely to the deprived condition and recall is partially impaired. This change probably has little significance for the habitual smoker who maintains plasma nicotine levels above some minimum level. The

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changes in sensory thresholds and hand tremor are inconsequential for most smokers.

2. Mood States

A large number of studies relating nicotine and mood have been carried out and so this review will be illustrative rather than exhaustive. It will focus on the mood states rather than the method of investigation and will discuss whether smoking does have sedative effects on anxiety and anger as smokers claim. In most cases the experimental studies have provided no evidence of nicotine absorption from cigarettes, and therefore it is not usually possible to separate the sedative effects of nicotine from the calming effect of the smoking ritual of cigarette manipulation.

a. Anxiety

Evidence for a sedative action of smoking comes from questionnaire studies, stress studies, personality tests of smokers and non-smokers, smoking abstinence studies and situations affecting smoking behaviour.

In a smoking motives survey, McKennell (1970) asked smokers about their mood states which might tempt them to smoke a cigarette and factor analysed the answers to extract the major factors which would produce smoking. One of these factors was "nervous irritation" smoking which included "smokes when anxious or worried" and "smokes when nervous" and also "smokes when angry". When the number of cigarettes smoked was controlled, female smokers exceeded the men for "nervous irritation" smoking. A factor analysis of smoking situations by Frith (1971) found a similar factor which he called high arousal smoking. High arousal smokers had a strong desire for a cigarette in stressful situations (eg an important interview) and women were more likely than men to smoke in these situations. Using a Smoking Motives Questionnaire, Russell et al (1974) and Warburton and Wesnes (1978) found that 93 per cent of smokers who attended a smoking clinic, 74 per cent of non-clinic smokers and 88 per cent of students said that they smoked when worried. Altogether, this evidence shows that smokers believe that smoking is beneficial to them when they are anxious.

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The bulk of the experimental evidence for smoking helping in stress situations has come from Stanley Schachter's laboratory. Nesbitt (1973) tested smokers, who used 20 or more cigarettes a day, and non-smokers on a shock tolerance test, on the assumption that it provided a measure of anxiety. Both groups were asked to smoke a 1.6 mg or 0.3 mg nicotine cigarette or puff on an unlighted cigarette. It was found that smokers who were smoking could take up to 2,450 microamps more after smoking and this effect was dose dependent. On the other hand, the non-smokers tolerated more shock in the no smoking condition but slightly less after the high nicotine cigarette. Assuming that shock tolerance is a measure of anxiety the simple explanation that smoking reduces anxiety does not fit this data because smokers who were only allowed to puff an unlighted cigarette tolerated less shock than non-smokers in the same condition. The latter finding suggests that nicotine from the smoke is more important than the smoking ritual in the effect on anxiety, but also that absence of nicotine in smokers results in more anxiety than for non-smokers. This finding could mean either that a nicotine deficit results in abstinence symptoms due to physiological dependence on nicotine or that smokers are constitutionally more anxious.

The latter possibility can be examined from personality studies of smokers. One influential theory of individual differences in behaviour is based on the dichotomy between extraversion and introversion and between neuroticism and stability and can be measured by a questionnaire such as the Eysenck Personality Inventory (Eysenck and Eysenck, 1964). People having high scores on neuroticism displays labile, emotional behaviour and are anxious, irritable, moody, restless, excitable and changeable. In contrast, stable people are calm and even tempered. There is less consistency in the evidence for a relationship between smoking and neuroticism, and Eysenck's studies of 6,000 men gave no evidence for a significant correlation (Eysenck et al, 1960; Eysenck, 1963 a). Rae's (1975) survey of 253 female students revealed no differences in the degree of neuroticism between non-smokers, ex-smokers, light smokers or medium smokers, but there were very few heavy smokers (over 15 per day) in his college sample. However, at least seven studies have suggested a positive relationship of smoking with neuroticism and this association is particularly strong for

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women smokers (Meares, et al, 1971; Waters, 1971; Dunnell and Cartwright, 1972).

In research at Reading University (Warburton, Wesnes and Revell, 1982) a questionnaire was given to 250 student male and female smokers to obtain information about the number of cigarettes smoked a day, the number of years that the individual had been smoking and the specific brands smoked. All the smokers completed the Eysenck Personality Inventory as well. Analysis of the data on number smoked per day and level of neuroticism of the whole group disclosed no association of smoke with neuroticism. However, for both sexes the distribution of number of cigarettes per day was bimodal with a separation around 15 cigarettes per day, in agreement with the results of a survey by Schachter (1978). This distribution suggests that there are two populations of smokers, light smokers and heavy smokers, as far as number of cigaretes smoked is concerned. The personality and smoking data were analysed separately in four groups, defined by sex and whether they were heavy or light smokers, so that the correlations within each of the four groups could reveal associations which may exist between smoking and neuroticism level. A positive correlation was found between the number smoked per day and the degree of neuroticism (ie the more neurotic smokers in each group smoked more cigarettes per day), even though the mean neuroticism scores of light and heavy smokers did not differ. Thus neuroticism was not related to whether a smoker was either a heavy smoker or light smoker, but within each sub-population, the number that he or she smoked per day was related to the degree of the individual's neuroticism. The heavy smokers were more extraverted than the light smokers and within each of these groups the male smokers were less extraverted than the females. In brief, light or heavy smoking was associated with extraversion, but within these two sub-populations, the number smoked per day was associated with neuroticism.

From these data one can speculate that the constitutional factors, which result in extraverted behaviour, determine whether a person becomes a light or heavy smoker whereas the factors that underlie neuroticism are not associated with heavy or light smoking, but influence the number smoked per day if an individual is a light or heavy smoker.

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Another interesting relationship emerged when correlations between personality and cigarette strength were considered. While extraversion scores were not correlated with the strength of cigarettes smoked, neuroticism scores were positively correlated for women, uncorrelated for male, light smokers and negatively correlated for male, heavy smokers so that the more neurotic females smoked higher delivery cigarettes.

Of course, these correlations were based on the machine-estimated yields of the cigarettes smoked and do not tell us how much nicotine was actually absorbed by the smoker. Self-report of depth of inhalation also varied among the personality groups. Deep inhalers had a higher mean neuroticism score than slight inhalers whose neuroticism scores were the same as non-smokers which suggests that smokers who score high on neuroticism absorb more nicotine.

In summary, we can safely conclude that the strength of cigarettes that are purchased by women smokers is related to their degree of neuroticism, and from the whole body of survey data that women buy cigarettes in order to help them cope with neuroticism.

Although this evidence is persuasive, Schachter might still argue that repeated exposure to nicotine had caused anxiety and a higher neuroticism score. Evidence against this argument is the lack of an overall correlation between number smoked and neuroticism. A second piece of evidence comes from a crucial study done by Cherry and Kiernan (1976; 1978) which has followed a cohort of 2,853 young people for 25 years. When they were 16 years old the subjects completed the Maudesley Personality Inventory before most of them had begun to smoke. At 20 years and 25 years of age they completed a smoking habits questionnaire and it was found that the cigarette smokers, as a group, were more extraverted and neurotic as we would have expected and those teenagers who smoked regularly before 16 years of age were more neurotic and more extraverted than smokers who did not smoke before they were 16 years old. A statistical analysis revealed that the two personality dimensions are independent and additive in their effect on the likelihood of becoming a habitual smoker and indicated that the constitution factors underlying anxiety produce smoking and not the other way round.

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As was pointed out earlier (Section III D) smokers can titrate for nicotine by varying the number of cigarettes smoked, their patterns of puffing and the amount of smoke inhaled. From these findings it can be predicted that smokers should titrate for nicotine depending on the situational demands, if they are smoking for nicotine to reduce anxiety. Schachter (1978) described two studies in which he studied stress and the number of cigarettes that were smoked. The subjects were tested with electric shock ostensibly to determine their tactile sensitivity. In the low stress condition smokers only received a low level of current to produce a tingle while the high stress group were occasionally given a painful shock. Schachter counted the number of cigarettes smoked between tests in the laboratory and found that the subjects smoked more cigarettes in the interval after the high stress condition than after the low stress condition ie when they were anxiously anticipating the next test series. Unfortunately, he did not collect any information about smoke generation and smoke manipulation.

In a recent study (Warburton et al, 1982) 48 first year undergraduates filled in a detailed diary on their smoking habits during a first year examination period and again 6 weeks later, after the examination results had come out. This design enabled us to compare the smoking behaviour of students in a high stress and a low stress period of their lives and find how people adjust their cigarette intake according to the situation. From the cigarette totals for the afternoons and evenings it was obvious that subjects smoked significantly more cigarettes at all times during the examination period than six weeks later. The mean number of cigarettes smoked during the morning before an afternoon examination was 80 per cent above the average number for mornings during the non-examination period and had increased by 29 per cent over the mean morning consumption for the examination period as a whole. The mean number of cigarettes smoked in an evening before an examination was higher than the mean for evenings in the non-examination period.

Subjects gave a subjective evaluation of their degree of inhalation and these reports followed exactly the same pattern as the data for number of cigarettes smoked ie, highly significant increases in degree

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of inhalation during the examinations with respect to the post-examination period. There was greater inhalation during the morning before an afternoon examination compared with the mean for mornings of the non-examination period. The degree of inhalation for the evening before a morning examination was significantly higher than the mean for an evening prior to a free day. Similarly, a comparison of the evening before a free day, within the examination period, with the mean for evenings, in the non-examination period, gave significant differences for degree of inhalation. Once again the individual data are highly consistent.

Thus the undergraduate students who took part in this study increased the number of cigarettes that they smoked quite dramatically when faced with examinations and the concomitant stress. They also felt that they were inhaling more than during the non-examination period. It can be assumed that the two questionnaires were fairly independent since the first was completed and returned six weeks before the second.

Some experimental evidence for titration by puffing was found by Ashton and Watson (1970) with subjects smoking in a driving simulation task. Subjects were tested in an easy driving task, a stressful driving task and at rest. In all situations they found that subjects puffed more frequently at the medium nicotine cigarettes (1.0 mg of nicotine on machine-estimated delivery) than the high nicotine cigarettes (2.1 mg nicotine on machine-estimated delivery), and butt analyses revealed that they took into their mouths nearly the same amount of nicotine from each brand. Interestingly, subjects generated more nicotine from the cigarettes during the more stressful test than the easier test, although the differences were not statistically significant, which suggests that individual smokers titrate the nicotine delivery from the cigarette according to the situation.

The Reading University research programme has examined the situation x individual x smoking interaction by studying the amount of nicotine taken by subjects in the vigilance test mentioned earlier (Warburton and Wesnes, 1978). Correlations were made between the neuroticism scores and the butt nicotine level from the test cigarettes. There was some evidence that the more neurotic subjects puffed harder than the more stable subjects on the first cigarette of

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the test period. However, a more interesting association was found between neuroticism and the change in smoking pattern over the session. A positive correlation was found between neuroticism and the difference in smoke generation between the first and last cigarette for both the low nicotine cigarette and the high nicotine cigarette, indicating that the more neurotic subjects smoke more intensely at the beginning of the session than at the end of the test. This result provides further evidence that one aspect of smoking behaviour is the outcome of the interaction of the situation and the individual.

Anxiety arises in situations of uncertainty when a person is subjected to an unpredictable pattern of stimuli or is faced with uncertainty about which response to choose, or both (Warburton, 1979) and this effect will be greater in more neurotic subjects in our test situation. Consequently, it can be argued that the more neurotic subjects found the test situation particularly stressful, and so they smoked more intensely because they have a greater need for nicotine in order to cope with the experimental test. This result is consistent with the trend in the data of Ashton and Watson (1970) that stress increased smoking intensity.

This research strongly suggests that smoking behaviour changes in stressful situations; smokers use more cigarettes, smoke them more intensely and inhale the smoke more deeply. The more neurotic subjects (those who are more anxious and susceptible to stress) show the most marked effects. The interesting question is: Does smoking help to cope with stress and improve behavioural efficiency? Accordingly we have analysed performance increments as a function of neuroticism and found that there was a direct association between the degree of neuroticism and the amount of performance improvement (Warburton and Wesnes, 1978). The latter association is consistent with data obtained by Kucek (1975) in an experiment where subjects were tested under conditions of information overload in which they were required to track a target and do mental arithmetic. A comparison of neurotic smokers allowed to smoke and neurotic smokers not smoking showed that smoking had a beneficial effect on the performance of neurotic subjects allowed to smoke.

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Nicotine is the most likely constituent of cigarettes for producing this improvement in performance, and in another vigilance study we tested nicotine tablets containing doses of nicotine in the range of those estimated as entering the smokers mouth in the previous study. For both females and males the improvement scores were directly correlated with neuroticism (Warburton and Wesnes, 1978). This signficiant association with neuroticism gives strong evidence for the hypothesis that nicotine is the sedative ingredient of cigarette smoke which is beneficial for performance, especially for the more neurotic subjects.

Inferences about the properties of a drug can often be made from the symptoms that occur when medication is terminated; for example the function of insulin for a diabetic person can be inferred from the symptom that occurs when injections are discontinued. Studies of withdrawal symptoms that follow cessation of smoking show that one of the major symptoms of cigarette withdrawal is anxiety (Nesbitt, 1972; Shiffman and Jarvik, 1976). It is more likely to occur among women because in this group there is a greater proportion of neurotic smokers (Guilford, 1966; Shiffman, 1979 b). Anxiety is also given as one of the major causes of relapse, especially among women (Shiffman, 1979 b). An analysis of the situations which resulted in a return to smoking was made by Marlatt (1979) and Shiffman (1971 a). Retrospective reports indicated that 80 per cent of these situations fell into three categories: coping with anxiety and other negative emotional states (43%), social pressure (25%) and coping with social stress (12%). Few of Marlatt's and Shiffman's relapsed smokers reported that physical withdrawal symptoms triggered the relapse which argues against the hypothesis that smokers carry on smoking because of physical dependence. In the Shiffman (1979 a) study, two thirds of the subjects were under stress at the time of relapse and anxiety was particularly common among ex-smokers who relapsed at work, which suggests that work-related anxiety was a contributory factor. Neurotics are more anxiety-prone and so it is not surprising that this group find it difficult to stop smoking or relapse if they do abstain (Cherry and Kiernan, 1978). These data on smoking to cope with stress fit neatly with studies which suggest that deprived smokers, as a group, are more likely to respond with anxiety in situations in which they are stressed. (Frankenhaeuser, et al, 1971; Myrsten, et al, 1972; Schachter, 1978).

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A large epidemiological study of British doctors has given some evidence which may indicate there are adverse consequences of smoking cessation (Lee, 1979). As a group, doctors have reduced their cigarette smoking over 20 years, and there has been some of the expected improvement in mortality rate from the so-called "smoke-related" diseases, but the overall death rate did not fall as much as one might have predicted from other groups of similar socioeconomic status. The reason for this discrepancy is that mortality from other causes has increased. In particular, stress-related deaths have increased relative to other professions in the equivalent social class, and more doctors have died from accidents, poisonings, suicide, and cirrhosis of the liver. Lee concludes that "the relative worsening in mortality from stress-related diseases may have been due partly to a possible adverse effect of giving up smoking if smoking had acted to reduce stress" (p 1538). This conclusion must be treated with caution because it is always very hazardous to argue from correlation to causality but, nevertheless, it is consistent with the previously cited research on smoking and stress.

In summary, a large body of evidence indicates that smokers smoke to reduce anxiety and smoke more and presumably take more nicotine when under stress. Subjects who are more prone to anxiety, ie scoring high on the neuroticism scale, smoke more intensely. Some experiments show that nicotine helps them cope with the situation better. Ex-smokers report that anxiety is one of the major problems of cessation and there is evidence that stress can lead to relapse. Those smokers who do abstain seem to be more prone to stress-related disorders and the full benefits of stopping smoking in terms of decreased mortality may not be achieved.

b. Anger

Another item that made up the "nervous irritation" factor of smoking in the McKennell (1970) questionnaire was anger. Thomas (1973) reported that on her "habits of nervous tension" questionnaire cigarette smokers and former smokers had higher levels of irritability and anger in comparison with lifetime non-smokers. When

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the smokers were divided into light (less than 20 a day) and heavy groups, the heavy smokers showed greater anger under stress than the light smokers. In two studies of smokers at a stop-smoking clinic and non-clinic smokers (Russell et al, 1974) and student smokers (Warburton and Wesnes, 1978), smoking when angry was one of the "top 10" reasons given for smoking by smokers attending a stop smoking clinic (83 per cent), non-clinic smokers (47 per cent) and student smokers (65 per cent). It appears from this consistency that a feeling of anger is a motive for smoking in some people.

Experimental studies of anger are difficult to conduct and no satisfactory experimehts on nicotine and anger in humans have been done. Schachter (1978) reports a study by Perlick which compared irritability in groups of "unrestrained" and "restrained" smokers the latter were trying to cut down their smoking and smoked less of the cigarettes. Each group were then exposed to aircraft noise and asked to rate the annoyance caused by the noise, after smoking either a 1.3 mg nicotine cigarette, a 0.3 mg nicotine cigarette or not smoking. It was found that unrestrained smokers, when deprived or smoking the low nicotine cigarette, were more annoyed than when smoking the medium nicotine cigarette. However, unrestrained smokers, when smoking the medium nicotine cigarette, were no better than non-smokers. The restrained group were just as irritated in all three conditions as the deprived or low nicotine, unrestrained smokers. There are at least two explanations for these results; either irritability is an abstinence symptom which is the consequence of nicotine dependence, or smokers are constitutionally more irritable and nicotine from smoking helps to reduce this feeling.

Studies of abstinence have shown hostility and aggressive behaviour increase markedly during abstinence (Mausner, 1980; Schachter and Rand, 1974; Shiffman and Jarvik, 1976). Anger is commonly reported as a factor triggering relapse among ex-smokers, and these relapses occurred in the absence of smoking-related cues such as "people around were smoking". (Shiffman, 1979 a). Clearly, the smoker who is deprived of nicotine is less calm. Evidence from a study by Thomas (1973), which showed similar scores for anger when stressed for smokers and ex-smokers, suggests that smokers are constitutionally more angry and irritable.

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In summary, smoking, and by inference nicotine, seems to have sedative effects for anger as well as anxiety.

3. Conclusion

These findings of enhanced psychological efficiency after nicotine are interesting from a psychopharmacological point of view because, although many drugs impair performance, it has proved difficult to find drugs which produce real improvements or even sustain performance in healthy, well-motivated subjects. The finding that nicotine can also act as a sedative makes the enhancement even more interesting because drugs with anti-anxiety action usually impair performance at effective doses. Thus nicotine is a unique substance because it combines both performance enhancement with anti-anxiety and anti-anger action.

While these findings alone are interesting, they assume even greater significance when they are considered in the light of the smoker's precise personal control over nicotine intake. The data in the preceding sections can be combined to argue that cigarette smoking can be regarded as self medication for certain groups. Studies of self medication suggest that people use those classes of drug which fulfil their own individual needs (Warburton, 1978) and the research presented here shows that people titrate nicotine to obtain a specific dose to fit their needs. Depending on the situation, smokers will adjust their smoking behaviour in terms of the number of cigarettes smoked, smoke generation and amount of smoke inhaled to control the nicotine levels reaching their brain and in this way their psychological state. Deprivation of cigarettes results in marked abstinence symptoms which are manifested as less efficient functions in certain situations, and so relapse is likely to occur in these contexts.

Consequently, the behaviour of a smoker is the outcome of a complex set of interactions. It is obviously determined, not only by the characteristics of the situation, but also by the personality of the individual. The personality characteristics will determine the way in which the individual selects and interprets information within the situation ie there is an interaction going on between individual factors

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and situational factors. If it is assumed that individual differences have a constitional basis (ie differences in the neurochemical pathways in the brain) then another complex interaction occurs when a drug is given to a person. Drugs do not affect human performance directly, but they produce changes in behaviour as a consequence of their interaction with endogenous chemicals within the body. Changes in neurochemical activity in the brain alter the way in which a person interacts with his environment and so performance not only reflects the nature of the drug but also the biochemical state of the person at that moment.

In sections (a) and (b) we have discussed the "stimulation" (low arousal) smoker and the "sedative" (high arousal) smoker as if they were homogeneous groups who self-medicated in the same way all the time. However, there must be differences in smoking behaviour as a function of the intensity of the individual-situation interaction, its duration and more probably its density (the product of intensity and duration). For example, a stimulation smoker may need less nicotine in brief, slightly boring tasks than a prolonged tedious situation, but conceivably the same smoking behaviour could occur during a brief, very boring, experience and a long, but moderately interesting task. In other cases smoking may not even be initiated until the intensity, duration or density of the interaction is at a critical level. Clearly, lighting a cigarette and the pattern of smoking behaviour depends on the individual-situation interaction.

An important extension of these concepts can be made on the basis of the observation that some smokers smoke in anticipation of a future need, before the situation has occurred or the critical stress level has been reached, and they are still coping. Here the smoking behaviour is very clearly a response to the individual's interpretation of the situation, his expectations about what may occur, rather than the objective characteristics of the situation. Smokers have learned that self-medication by smoking will enable them to function more efficiently on some tasks and will help them avoid the undesired consequences of other situations and so anticipatory smoking can be seen as a rational coping strategy on the basis of their past experience.

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Advocates of abstinence and the operators of stop smoking clinics have disregarded this information. They have focused on the smoke-related diseases and not considered the benefits of smoking. The smoking habit must be considered from the point of view of the smoker. If he smokes and absorbs nicotine he will function more efficiently now, but risks impaired health in the future. If he abstains he loses the benefit of nicotine and may have better health in the future. It is not surprising that many smokers choose to continue smoking, that abstaining smokers relapse, and stop smoking programmes have a conspicuous lack of success. In the next section we will consider nicotine in the context of some other substances which have been used by people to control their mood or to help them perform better.

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